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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,566	01/23/2004	Richard Franklin	20342/1202529-US1	3220

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EXAMINER	
HUGHES, ALICIA R	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,566	FRANKLIN, RICHARD	
	Examiner	Art Unit	
	ALICIA R. HUGHES	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2009*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,12,13 and 17-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,12,13 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 2, 12-13 and 17-22 are pending. Applicants cancelled claims 3, 6-9, 14, 15, 24-25, 29, 31, 33-34, 36 and 50 in their response dated 10 March 2010. Applicants' arguments, filed on 10 March 2010, have been fully considered and are deemed to be persuasive regarding the previous rejection. Rejections and objections not reiterated from previous Office Actions are hereby withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections – 35 U.S.C. §103

I. First 103 Rejection

Claims 2, 12, 13 and 17-20 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,194,420 [hereinafter referred to as "Lang"], in view of U.S. Patent No. 6,221,383 [hereinafter referred to as "Miranda et al"], and in further view of U.S. Patent No. 6,024,975 [hereinafter referred to as "D'Angelo et al"] and in further view of Solberg, Lawrence, "Therapeutic Options for Essential Thrombocythemia and Polyctyhemia Vera, *Seminars in Oncology*, Vol. 28, Issue 3, Supplement 10, page 10-15 (2002)[hereinafter referred to as "Solberg"] as evidenced by Bonkovsky, Herbert L., et al, "Drug-Induced Liver Injury," *Zakim and Boyer's Hepatology, 5th Edition, pages 503-550* (2006)[hereinafter referred to as "Bonkovsky et al"] and Ammar, H.O. et al, "Design of a Transdermal Delivery System for Aspirin as an Antithrombitic Drug," *International Journal of Pharmaceutics*, Vol. 327, pages 81-88 (2006)[hereinafter referred to as "Ammar et al"].

The Applicant argues that there are unexpected results that render the instant invention non-obvious and cites the declaration of Dr. Richard Franklin to support the premise that Applicant has unexpectedly discovered that transdermally administering anagrelide to treat thrombocythemia minimizes the adverse cardiovascular side effects observed when anagrelide is administered orally and that the same is not "trivial" as previously, a number of patients were unable to tolerate the drug and cites *Eibel Process Co. v. Minnesota & Ontario Paper Co.* to support his position.

The teachings of Lang, Miranda, and D'Angelo as set forth in this Office's Action dated 19 April 2007, 16 April 2008, 17 November 2008, 01 April 2009 and 10 March 2010 are incorporated herein by reference and for the reasons set forth therein are applied to the same claims presently and in entirety.

Solberg teaches that aspirin, like anagrelide, is useful in the treatment of thrombocythemia (Solberg, Jr., page 11, chart and Col. 2 through page 12, Col. 1 and chart on pages 12 and 13) and there is a correlation between the treatment of thrombocythemia with aspirin and anagrelide and aggravation of cardiovascular risk factors that the literature does seek to solve (Solberg, Jr. at Page 15, Col. 1). Furthermore, the prior art appreciates the use of drugs transdermally to treat antithrombotic conditions (Ammar et al Abstract and pages 86 and 87 in their entirety).

It is well-known in the pharmaceutical art that most chemicals are ingested orally and absorbed primarily in the small intestine with some undergoing initial metabolism within the gastrointestinal tract. *See* Bonkovsky, Page 503, Col. 1, specifically. However, it is not in these places but rather when compounds and/or metabolites enter the splanchnic blood where they are

eventually delivered via portal circulation to the liver, that we have the effect of first pass metabolism (where bioavailability is most important). *Id.*

As noted prior, it has been widely known for some time now that transdermal delivery of drugs generally enable with immediacy pass of the first liver metabolism, bypassing the GI tract and small intestine and increasing bioavailability while at the same time *decreasing various side effects*. *Please see*, e.g., Ammar, H.O. et al, "Design of a Transdermal Delivery System for Aspirin as an Antithrombitic Drug" *at* page 87 Col. 2. Further, orally administered drugs, particularly aspirin and others known to treat thrombocythemia, require high and frequent dosing because they undergo extensive presystemic hydrolysis in the gut and liver. *Id.* As a result of the teachings of Anmar given the state of the art generally regarding the transdermal delivery of drugs, in the absence of express evidence to the contrary, transdermal administration of the same reduces this extensive presystemic hydrolysis resultant from oral administration, provides enhanced bioavailability and as appreciated in the art, reduces cardiovascular and gastrointestinal side effects. *Please see, e.g.*, Anmar et al at page 87, Col. 2.

Thus, while the Examiner does appreciate the Applicants' argument, in light of these findings, the same is not persuasive. Further, the limitation, "thereby reducing the plasma concentration of 3-hydroxy anagrelide compared to a patient orally administered the equivalent amount of anagrelide" in claim 2 and the correlative argument that the same is a surprising result that enables one to circumvent adverse side-effects observed from administering anagrelide orally is not found persuasive.

As stated in a previous action, this limitation is a mere function that necessarily flows from the method claimed, because Applicant has elucidated an inherent biochemical mechanism

regarding the administration of anagrelide. In contrast to what the Applicant has cited from cites *Eibel Process Co. v. Minnesota & Ontario Paper Co*, it is well understood by those of ordinary skill in the art that "the discovery of a previously unappreciated property of a prior art composition or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F. 3d 1342, 1347 (Fed. Cir. 1999). Therefore, the claiming of a new use, a new function, or an unknown property, which is necessarily present in the prior art does not make the claim patentable. Rather, it is incumbent upon the Applicants to "prove that subject matter shown to be in the prior art does not possess characteristics relied on," *In re Fitzgerald*, 205 USPQ 594, by the presently claimed invention. The Applicants have not met this burden.

In view of the foregoing, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to transdermally administer anagrelide to a patient with thrombocythemia to minimize first liver metabolism and thereby reduce the plasma concentration of 3-hydroxy anagrelide compared to a patient orally administered the equivalent dosage of the same.

One of ordinary skill in the art would have been motivated to combine the teachings of Lang, Miranda et al, D'Angelo and Solberg as evidenced by Bokovsky et al and Ammar et al to conclude that the combination of anagrelide or its salt form, along with a skin permeation enhancer, administered transdermally so as to avoid the first pass liver metabolism would be effective in the treatment of essential thromboycythemia.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art that the administration of a single or multiple layer formulation of an effective amount of

anagrelide or an anagrelide salt and a menthol acting has a skin permeation enhancer with acrylic adhesive with a surface area ranging from 1 to 200 square centimeters acting together as a transdermal delivery device would be effective for treating essential thrombocythemia.

Accordingly, for the above reasons, the claims are deemed properly rejected.

II. Second 103 Rejection

Claims 21-22 are rejected under 35 U.S.C. 103(a) as being obvious over Lang in view of D'Angelo and in further view of U.S. Patent No. 5,133,972 [hereinafter referred to as "Ferrini et al"].

The Applicant now argues that there are unexpected results that render the instant invention non-obvious and cites the declaration of Dr. Richard Franklin to support the premise that Applicant has unexpectedly discovered that transdermally administering anagrelide to treat thrombocythemia minimizes the adverse cardiovascular side effects observed when anagrelide is administered orally.

The teachings of Lang and D'Angelo et al, *supra* and as stated in this Office's Actions of 19 April 2007, 16 April 2008, 17 November 2008, 01 April 2009 and 10 December 2009 as well as the arguments herein, *supra*, are incorporated herein by reference, in total. The teachings of Ferrini et al, as noted in this Office's previous actions are incorporated herein by reference in total, also.

The teachings of Bonkovsky et al, Ammar et al and Solberg, *supra*, are incorporated herein by reference in their entirety, also. In light of the foregoing and for the reasons made previously of record, the claims are deemed properly rejected.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia Hughes whose telephone number is 571-272-6026. The examiner can normally be reached from 9:00 A.M. until 5:00 P.M. on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax number for the organization where this application is proceeding is assigned 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alicia R. Hughes/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614